Remarks

I. The Claims

Upon entry of the foregoing amendments, claims 1, 5-19 and 21 are pending in the application, with claim 1 being the sole independent claim. Claim 1 is sought to be amended. No new matter is added by way of these amendments. It is respectfully requested that the amendments be entered and considered.

Support for the amendment of claim 1 can be found, *inter alia*, throughout the specification, *e.g.*, original claims 1 and 20.

II. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1, 5-19 and 21 were rejected under 35 U.S.C. § 112, first paragraph, because:

> the specification, while being enabling for treating a carcinoid tumor with a replication-competent, oncolytic strain of Newcastle Disease Virus (NDV), does not reasonably provide enablement for any replication-competent strain of NDV.

(Advisory Action, page 2.) Applicants respectfully disagree.

Even if it is shown that some NDV strains do not have anti-tumor effects, "[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984)". (MPEP 2164.08(b), Eighth Edition, September 2007.)

Even though the evidence presented below conclusively supports that the claimed invention meets the enablement requirements, Applicants remind the Examiner that "[t]he evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art." (MPEP 2164.05; underlining in original.) Further, the MPEP states, "the scope of enablement must only bear a 'reasonable correlation' to the scope of the claims. See, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)." (MPEP §2164.08)

A. The Scope of the Present Claims is Enabled

The Examiner has taken the position that a substantial portion of replication-competent NDV strains will not result in treatment of a carcinoid syndrome as presently claimed. Applicants respectfully disagree with this position. However, even if this position has merit, it is not relevant to the enablement of the presently claimed invention. Claim 1, from which all other claims ultimately depend, recites "administering to the subject an amount of a therapeutic virus". (underlining added.) Therefore, if a particular NDV strain will not result in treatment of a carcinoid syndrome, then it is not a "therapeutic virus", and is thus excluded from the claimed subject matter. Of course it is irrelevant if excluded subject matter is enabled.

Additionally, using the teachings of Applicants' specification, one skilled in the art can readily determine, without undue experimentation, if a particular NDV strain is a therapeutic virus with regards to the presently claimed invention. Since practicing the presently claimed invention does not require undue experimentation, the presently claimed invention is enabled.

B. Most, if Not All, NDV Strains Selectively Kill Tumor Cells

In the case that the Examiner maintains the rejection in spite of Section II.A., above, Applicants present the following. The Examiner has taken the position that Applicants' specification is enabling for treating a carcinoid tumor with a replication-competent, oncolytic strain of Newcastle Disease Virus (NDV), but does not reasonably provide enablement for any replication-competent strain of NDV. (Advisory Action, page 2.) The rejection focuses on the incorrect assumption that non-oncolytic or non-lytic NDV strains will not lead to the destruction of tumor cells and that an NDV strain that does not directly lyse the tumor and/or spread to other tumors cells could not treat a mammalian subject having a tumor. Applicants respectfully disagree with this position.

The Examiner states that there are "no working examples showing anti-tumor effects with nonlytic strains of NDV" (Advisory Action, page 7) and that "[g]rowth [of NDV] in tumor cells does not translate into anti-tumor abilities. There are strains of NDV that selectively grow on tumor cells versus non-tumor cells but do not cause cell lysis. For example, NDV strain 20Z

(discussed above) grows on tumor cells (not non-tumor cells) but is not oncolytic and does not show anti-tumor properties (see Cassel et al., Discussion)." (Advisory Action, pages 6-7.) Applicants respectfully disagree. As discussed in detail below, non-lytic NDV strains still cause destruction of the infected tumor cell in a mammalian subject and can cause a "bystander effect" that kills uninfected tumor cells, *e.g.*, through an immune response directed against the tumor cells. Therefore, a non-lytic NDV strain can be a "therapeutic" virus as recited in the present claims.

Previously, the Examiner has asked "[h]ow would applicants' claimed method work with a non-oncolytic strain of NDV such as 20Z?" (Office Action, June 20, 2007, page 7.) In response, it is known in the art that both lytic and non-lytic NDV strains kill the tumor cells they infect. "There are many different strains of NDV, and they have been classified as either lytic or non-lytic for human cells. Lytic strains and non-lytic strains both appear to replicate much more efficiently in human cancer cells than they do in most normal human cells." (Newcastle Disease Virus, (PDQ®), General Information, National Cancer Institute, Last Modified December 4, 2007, http://www.cancer.gov/cancertopics/pdq/cam/NDV/HealthProfessional/page3, fourth paragraph; provided herewith as part of an Information Disclosure Statement (IDS).) Therefore, NDV strains have been divided into two groups (lytic and nonlytic) and both groups replicate preferentially in human cancer cells.

Additionally, "non-lytic strains of NDV kill infected cells more slowly, with death apparently the result of viral disruption of normal host cell metabolism" (*Id.*, page 1, fifth paragraph; underlining removed.) and "cells infected with a nonlytic strain of NDV will remain intact in the body long enough to generate these more effective immune responses." (*Id.*, page 2, second paragraph.) Non-lytic NDV strains have been shown, *inter alia*, to induce tumor cell specific immune responses. Therefore, one skilled in the art, based on the teachings of Applicants' specification would conclude that non-lytic NDV strains can be utilized as a therapeutic virus with regards to the claimed invention.

Several studies have been performed demonstrating tumor cell killing by non-lytic NDV strains, *e.g.*, see Schirrmacher *et al.* 2001 (Int J Oncol. 18(5):945-52) and Schirrmacher *et al.*

1999 (Gene Therapy, 6:63-73), both provided herewith as part of an IDS. In fact, Schirrmacher *et al.* 2001 demonstrated in one model that the non-lytic Ulster strain "showed stronger antitumor activity than the lytic strain 73T." (see abstract.)

In the June 20, 2007 Office Action, the rejection identified the La Sota strain of NDV as an example of a non-lytic strain of NDV. (Office Action, June 20, 2007, page 7, line 3.) As discussed in Applicants' Reply of August 20, 2007, there is no reason to doubt that non-lytic NDV strains, such as the La Sota strain, could be useful as an antitumor therapeutic agent. Krishnamurthy, *et al.* report:

> [w]e then examined four other strains of NDV (Kansas, California, La Sota, and Australian-Victoria) . . . . We observed that the growth of these strains in normal and tumor cells was comparable to that of the 73-T strain. Thus, different strains of NDV are inherently tumor selective and may be equally useful as antitumor therapeutic agents.

(Krishnamurthy, *et al.*, J. Virol. (2006) 80(11): 5145-5155 at 5148, left column; underlining added.) (of record). The findings of Krishnamurthy are inconsistent with the position of the rejection that a non-lytic NDV strain such as La Sota cannot have anti-tumor activity.

As further support that one skilled in the art recognizes non-lytic NDV strains as potential therapeutic viruses, as presently claimed, Applicants refer the Examiner to Freeman *et al.* (Molecular Therapy, 13(1):221-228 (2006)), provided herewith as part of an IDS. Among other things, Freeman *et al.* demonstrates anti-tumor effects in humans using the lentogenic NDV-HUJ strain (non-lytic). Freeman *et al.* states, "[i]n most tissues, lentogenic strains produce defective progeny, are monocyclic, and cannot easily spread between tissues." (page 226, first column.) In spite of these characteristics, Freeman *et al.* demonstrates that a non-lytic strain of NDV achieved anti-tumor effects in humans. Additionally, "[t]he lentogenic LaSota and Ulster strains were also shown to induce anti-tumor cytotoxicity in mouse macrophages and human monocytes". (*Id.*, page 226, second column.) Therefore, it is clear that non-lytic NDV strains exhibit anti-tumor effects in mammals, such as humans. In fact, Freeman *et al.* refers to NDV in general as having "a long history as a broad-spectrum oncolytic agent that can destroy tumor cells and stimulate the immune system". (Freeman *et al.*, page 221.)

Furthermore, Applicants point to the *ClinicalTrials.gov, Newcastle Disease Virus (NDV) for Cancer Patients Resistant to Conventional Anti-Cancer Modalities* (ClinicalTrials.gov, Identifier: NCT00348842; of record) which states that "[b]oth oncolytic and non-oncolytic NDV were used clinically in hundreds of patients with different types of cancer worldwide." (page 1, second paragraph, underlining added.) Therefore, those skilled in the art (*e.g.*, at governmental agencies) believe that NDV strains, in general, will lead to the destruction of tumor cells or else these clinical trials would have never been proposed or approved.

C. Documents Cited by the Examiner Do Not Support Enablement Rejection

The Examiner seems to refer to Sinkovics *et al.* as showing that "only certain NDV strains were labeled as 'antineoplastic agents' for human tumors". (Advisory Action, page 2; underlining added.) Applicants respectfully disagree. Applicants believe the Examiner's statement is referring to the recitation by Sinkovics *et al.* that,

> [t]his report . . . describes the early historical events that led to the recognition that certain NDV strains are 'antineoplastic agents' for human tumors".

(Sinkovics *et al.*, page 2.) This statement does not mean that certain NDV strains were not shown to be 'antineoplastic agents' for human tumors.

The Examiner also refers to the quote from Sinkovics *et al.* that states,

> [v]arious NDV strains differ widely in their biological effects including oncolysis and without specific studies of a given NDV strain, generalizations that it is oncolytic just because it is a NDV strain are invalid and unacceptable.

(page 11, column 1.) Additionally, Sinkovics *et al.* states,

> the matter of viral oncolysis was simplified by presuming that directly oncolytic viruses lose their oncolytic efficacy consequentially to humoral antiviral immunity of the host, whereas when an incompletely replicating or not cytolytic virus establishes a persistent 'carrier culture' relationship with a tumor, antiviral immune faculties (cytolytic antibodies; immune T cells) attack and eliminate tumor cells expressing viral antigens.

(page 6, bottom of the second column.) Therefore, in light of these statements and all of the evidence that non-lytic NDV viruses exhibit anti-tumor effects, the term "oncolytic" as used in this statement by Sinkovics *et al.* must be interpreted as meaning being able to replicate and

produce infectious virus in tumor cells. With this in mind, Sinkovics *et al.* is merely stating that a given NDV strain must be evaluated for this characteristic.

The Examiner has cited Sinkovics *et al.*, Wildner and Cassel *et al.* for the proposition that NDV strains do not exhibit anti-tumor properties. However, none of these references provide any experimental results demonstrating that any particular NDV strain lacks anti-tumor effects. In contrast, Applicants have clearly presented herein evidence of anti-tumor effects with non-lytic NDV strains and NDV strains in general.

D. Summary

The Examiner has rejected the present claims as not enabled because Applicants' specification "does not reasonably provide enablement for any replication-competent strain of NDV". (Advisory Action, pages 2 and 7.) As discussed above, the subject matter of the present claims include "administering to the subject an amount of a therapeutic virus". (underlining added.) Therefore, if a particular NDV strain is not a "therapeutic virus", then it is excluded from the claims. One skilled in the art can readily determine, without undue experimentation, if a particular strain of NDV is a therapeutic virus with regards to the presently claimed invention.

Additionally, Applicants have shown above that non-lytic strains of NDV generally exhibit anti-tumor activities. Previously, the Examiner challenged Applicants to explain "[h]ow would applicants' claimed method work with a non-oncolytic strain of NDV such as 20Z?" (Office Action June 20, 2007, page 7.) Applicants have provided numerous examples of anti-tumor properties of non-lytic virus, whereas the Examiner has not provided any experimental evidence that any NDV strains do not possess anti-tumor cell properties. As discussed above, NDV strains have been classified into two groups, lytic and non-lytic on human cells, and both groups have been shown to preferentially kill tumor cells.

In view of the above, Applicants respectfully request the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, first paragraph.

III. NO DOUBLE PATENTING

Claims 1, 5-8 and 16-17 have been provisionally rejected for alleged obviousness-type double patenting over claims 1-3, 6, 7, 19, 22-25 and 27 of U.S. Patent No. 7,056,689. (Advisory Action, page 7.)

Claims 13-15 have been provisionally rejected for alleged obviousness-type double patenting over claims 157-161, 163-170, 172, 174, 183, 196-219 and 230-232 of copending Application No. 09/958,809; claims 1-6, 12, 17, 21, 22, 26-28 and 34 of copending Application No. 10/518,732, claims 1-13 of copending Application No. 10/547,654 and over claims 1-13 of copending Application No. 10/548,057. (Advisory Action, pages 8-10.)

Claims 1, 5-8, 13, 16 and 17 have been provisionally rejected for alleged obviousness-type double patenting over claims 1-3, 6-8, 50, 51, 63-65, 69, 70, 73, 115-120, 132, 134, 136 and 144 of copending Application No. 10/167,652. (Advisory Action, page 9.)

Claims 1, 5-8 and 16-18 have been provisionally rejected for alleged obviousness-type double patenting over claims 14, 17, 18, 21, 22, 33, 34, 36-39 and 41 of copending Application No. 11/441,201. (Advisory Action, page 11.)

All of the obviousness type double patenting rejections are respectfully traversed.

A. Applicants' Previous Amendments Were Not Addressed

In Applicants' Reply of April 8, 2007, claim 1 was amended to incorporate elements of original claim 20. Claim 20 has not been rejected for alleged obviousness-type double patenting. Therefore, claim 1 as amended should not be the subject of obviousness-type double patenting. Applicants respectfully submit that the Examiner has not addressed this situation in either the Office Action of June 20, 2007 or the present Advisory Action. Therefore, Applicants respectfully request clarification on this situation.

B. Obviousness Type Double Patenting Rejection Must Include An Obviousness Analysis

An obviousness type double patenting rejection must be based on an obviousness analysis. Reasons must be given for concluding that the invention defined in a claim at issue

would have been an obvious variation of the invention defined in a claim in a patent or copending application. The Examiner has not, as required (MPEP § 804), provided proper reasons why the rejected claims would be considered obvious variations of the claims in the cited patent or co-pending applications.

The only reason given in support of the rejection is that the reference claims allegedly "encompass" or "overlap" with the claims of the subject application, but as the courts have held, that is insufficient reason to sustain a prima facie case of nonstatutory double patenting. As stated by the CCPA, "[t]o use the words of which the board seemed to be enamored, the broader claim 'embraces' or 'encompasses' the subject matter defined by the narrower claim. . . . This commonplace situation is not, per se, double patenting as the board seemed to think." *In re Kaplan*, 789 F.2d 1574, 1577-8, 229 USPQ 678 (Fed. Cir. 1986), citing *In re Sarett*, 51 C.C.P.A. 1180, 327 F.2d 1005, 1014, 1015, 140 U.S.P.Q. (BNA) 474, 482, 483 (CCPA 1964)." Similarly the Board has noted that ". . . a mere genus-species or broad-narrow relationship between pending and patented claims is not a litmus test for resolving the question of double patenting of the obviousness type." *Ex parte Michno*, No. 93-0877, 1993 Pat. App. LEXIS 38, *6 (BPAI 1993).

Additionally, the MPEP states,

> [d]omination and double patenting should not be confused. They are two separate issues . . . . Domination by itself, i.e., in the absence of statutory or nonstatutory double patenting grounds, cannot support a double patenting rejection. *In re Kaplan,* 789 F.2d 1574, 1577-78, 229 USPQ 678, 681 (Fed. Cir. 1986); and *In re Sarrett*, 327 F.2d 1005, 1014-15, 140 USPQ 474, 482 (CCPA 1964).

(MPEP § 804 @ 800-19.)

Therefore, since the Examiner has only referred to the reference claims as encompassing or overlapping with the claims of this application, a *prime facie* case of obviousness has not been established. In view of the above, Applicants respectfully request the Examiner reconsider and withdraw the obviousness type double patenting rejections.

Conclusion

It is not believed that extensions of time are required beyond those that may otherwise be provided for herein or in accompanying documents. However, if additional extensions of time are necessary to prevent abandonment of this application, The United States Patent and Trademark Office is hereby authorized to charge any fee deficiency required to prevent abandonment of the current application or credit any overpayment to Deposit Account 50-1677.

Applicants believe that a full and complete Reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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